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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	05/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 05/01/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/718,163	DEBENEDETTI ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 1/19/2007.

The amendment filed 1/19/2007 is acknowledged and has been entered.

Status of the Claims

Claims 1-56 are currently pending in the application and are addressed herein.

Applicant's election without traverse of species 2 (a method for selectively expressing a toxin in a cell comprising administering a messenger RNA sequence as in claims 13-24,41-56), and the species lung cancer in the reply filed on 10/18/2006 is acknowledged.

After further consideration, and in view of applicants' assertion that administration of an mRNA sequence encompasses administering a DNA sequence which encodes such a mRNA (e.g., see applicants' paper filed 10/18/2006, pages 7-8), the election of the species indicated as 1) administering a DNA and 2) administering an mRNA is withdrawn.

Accordingly, claims 1-56 are examined herein.

Priority

Applicants are asked to review the first line of the specification and to make any necessary changes. It is noted that the status of the prior application should be included in the priority information indicated in the first line of the specification.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/8/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

Claims 2, 14, 26, 42 objected to because of the following informalities: These claims recite the phrase "folded state free energy AG <about –50Kcal/Mol". However, it is believed that the phrase should be "folded state free energy ΔG <about –50Kcal/Mol". This is considered to be a typographical error, and the claims are examined as if the phrase was written as "folded state free energy ΔG <about –50Kcal/Mol". Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites the phrase, "The method as recited in claim 2$" in line 1. Therefore, it is unclear which of the other claims claim 26 depends from. Claims 27-40 are rejected because they depend on claim 26.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 13, 16-24 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn methods which encompass administering a nucleic acid sequence to a cell wherein the nucleic acid sequence comprises any untranslated sequence that inhibit translation in absence of eIF4E and allow translation in the presence of eIF4E. It is noted that the claims do not require any specific sequence. Therefore, the claims encompass a potentially enormous genus of untranslatable sequences that inhibit translation in absence of eIF4E and allow translation in the presence of eIF4E. This large genus is represented in the specification only by the disclosure that the sequence is "a relatively long palindromic oligonucleotide sequence that is self-complementary" (see p. 7, first paragraph; and p. 23. first paragraph), and that the untranslatable sequence comprises a hairpin secondary structure conformation having a stability measured as folded state free energy of $\Delta G \leq$ about –50 Kcal/Mol (e.g. See originally filed claim 2). Thus, applicants have only disclosed a vague description of a structure characteristic of a genus comprising potentially millions of different possibilities considering the vast number of sequences which might inhibit translation in absence of eIF4E and allow translation in the presence of eIF4E.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, a description of the required function of the sequences is disclosed (the ability to inhibit translation in the absence of eIF4E and to allow translation the presence of eIF4E). However, there is no specific description of the structure of any species (i.e. a nucleic acid sequence) of the genus. The only guidance for the identification of sequences that meet the functional limitations is the disclosure that the sequence is "a relatively long palindromic oligonucleotide sequence that is self-complementary", and that the untranslatable sequence comprises a hairpin secondary structure conformation having a stability measured as folded state free energy of $\Delta G \leq$ about –50 Kcal/Mol.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, there is only a vague description of a nucleic acid sequence that would inhibit translation in the absence of eIF4E and allow translation in the presence of eIF4E.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or disclosure demonstrating conception or written description of any nucleic acid sequence that has the ability to inhibit translation in the absence of eIF4E and allow translation in the presence if eIF4E other than the untranslatable sequences that and that the untranslatable sequences which comprises a hairpin secondary structure conformation having a stability measured as folded state free energy of $\Delta G \leq$ about –50 Kcal/Mol.

Claims 1-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> Methods comprising administering directly to a cell a mRNA sequence or a DNA sequence encoding said mRNA sequence, wherein the mRNA sequence comprising a translatable sequence encoding a toxin and an untranslatable sequence that inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eIF4E but which allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eIF4E relative to normal cells and wherein the untranslatable sequence comprises a hairpin secondary structure conformation having a stability measured as folded state free energy of $\Delta G \leq$ about –50 Kcal/Mol;

does not reasonably provide enablement for the full scope encompassed by the claims; specifically the claims are not enabled for any route of administration other than administration directly to the target cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods which encompass administering a either a mRNA sequence or a DNA encoding the mRNA, wherein the mRNA sequence comprising a translatable sequence encoding a toxin and an untranslatable sequence that inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eIF4E but which allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eIF4E relative to normal cells. The specification discloses that the methods are useful for treating cancer in a subject and claims 25-56 are explicitly drawn to treating cancer in a subject. Therefore the claims encompass the use of a nucleic acid sequence for therapeutic purposes (i.e. gene therapy).

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims encompass a DNA sequence that when transcribed produces an mRNA comprising a UTR. The UTR can be any sequence that allows translation of the mRNA in the presence of eIF4E, but does not allow

translation of the mRNA in the absence of eIF4E. The UTR can be operably linked to any type of toxin. Furthermore, the claims encompass the treatment of any type of cancer in any animal species, including humans.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed.

Regarding the administration of the therapeutic nucleic acid to a part of the body other than site of the target cells (in this case, the tumor cells), it is well established in the art that delivery is one of the key problems of gene therapy. For instance, regarding gene therapy in general, Anderson (Nature 1998; 392(suppl):25-30) teaches,

> The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems regarding gene therapy in general. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, Greco (Frontiers in Biosci. 2002; 7:d1516-1524) teaches,

> The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection. (see p. 1517, paragraph bridging columns 1-2).

Indicating that direct delivery of the nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate cells.

The claims encompass a type of gene therapy known as gene directed enzyme prodrug therapy (GDEPT). GDEPT is well known in the art. In general, GDEPT is a two-stage process involving step 1: the administration of a vector encoding a foreign enzyme (e.g. TK) that is selectively expressed in tumor cells, followed by step 2: delivery of a prodrug (e.g. GCV) which is convert into an active (i.e. toxic) form by the enzyme of step 1.

Methods using a GDEPT system utilizing TK/GCV for the treatment of solid tumors were well known in the art at the time of filing (see Kirn et al. Trends in Mol. Ned. Vol. 8, Suppl: p. S68-S73; 2002). The known systems utilize tumor-specific promoters to confer tumor-specific expression of TK, which selectively express TK in the tumor cells. The instant invention utilizes a similar system; however, rather than using a tumor-specific promoter to regulate the expression of TK, the applicants have used an element that regulates the expression of a toxin (such as TK) at the translational level. Specifically, the instant invention involves using an mRNA comprising a UTR that confers tumor-specific translation/expression of a toxin. The UTR allows the translation of the toxin in the presence of eIF4E (a polypeptide involved in

initiating translation) and inhibits translation in the absence of eIF4E. EIF4E is present at low concentrations in wild-type cells and elevated in tumor cells.

Regarding the efficacy of GDEPT therapy, Kirn et al. teaches,

> "Several advantages [of GDEPT] can be defined: enhanced selectivity of toward cancer cells, amplification effects, and bystander cell death. However, technical hurdles related to the delivery of the foreign gene by viral or non-viral vectors remain to be overcome before reaching therapeutic success. Thus the main requirement for the future is efficient targeting and delivery." (Emphasis added; see p. S72 under Concluding Remarks).

Thus, Kirn et al. teaches that targeting and delivery of the therapeutic gene is a critical obstacle that must be addressed, which is consistent with the teachings of Anderson, Crystal and Greco, as indicated above.

Working Examples and Guidance in the Specification

The specification discloses working examples that a DNA sequence (i.e. UTK) can be administered to mouse mammary cells in vitro (both wild-type and tumorigenic cells) resulting in an increased cytotoxic effect on tumorigenic cells compared to the controls when GCV is administered (see Table 2, p. 12). Similar effects are seen in human breast cells in vitro (see Example 4, p. 12). The specification also discloses by example that the DNA sequence (i.e. UTK) can be administered to tumor cells in immunologically impaired mice (in vivo) by direct administration and by systemic administration, resulting in a tumor-specific toxic effect compared to the controls (see Examples 5 and 6, p.14-18).

However, the working examples compare effectiveness of the claimed DNA sequence (i.e. UTK) to a control DNA sequence that constitutively expresses the toxin (TK) in all cell types. It was known in the art that tumor-specific expression of the toxin was critical for effective therapeutic treatment (see above). The GDEPT systems known in the art utilized

tumor-specific promoters to confer tumor-specific expression of TK. However, this type of system is still plagued by unpredictable and unreliable results (see above). In order to overcome the unpredictability of tumor treatment using a GDEPT system recognized in the art, the specification would have to show examples that the instant invention overcomes the recognized obstacles and shortcomings. To do this the working examples would have to show that regulating the expression of the toxin (TK) at the translational level overcomes the art recognized problems regarding systemic administration of the nucleic acid in subjects that have a fully functional immune response. However, the working examples only show systemic administration of a DNA to an immunocompromised mouse. There are no working examples show systemic administration of a DNA to a mouse that has a fully functional immune system. Furthermore, there are no working examples showing systemic administration of an mRNA to any subject, which is encompassed by some of the claims. Therefore, there are no working examples showing that the claimed invention overcomes the unpredictability recognized in the art.

Quantity of Experimentation

The art recognizes that a high level of experimentation is required for the development of a viable and efficacious GDEPT cancer therapy. For example, Kirn et al. (Trends in Mol. Ned. Vol. 8, Suppl: p. S68-S73; 2002) teaches that the progression of suicide gene therapy approaches to the clinic will require further investigations into effective tumor targeting and vector delivery (see p. S70, second paragraph). Furthermore, Anderson, Crystal and Greco all provide evidence

that systemic delivery of a therapeutic nucleic acid sequence is unpredictable because of, among other things, the host's immune response.

The quantity of experimentation to determine the reliability and efficacy of the proposed GDEPT system is very large. For example, considering the broadest claims encompass any UTR that selectively allows translation in cells the overexpress eIF4E, additional experimentation is required to identify the functional UTRs encompassed by the claims.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method to its full scope is undue.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

2. Claims 1-25, 41-56 are rejected under 35 U.S.C. 102(a) as being anticipated by DeFatta (Dissertation, catalogued and placed on the shelf March 20, 2001; note this reference was cited

and supplied by Applicants in prior Application 09/916,017; therefore although it is cited by the Examiner here, it will not be provided to applicants as they should already be in possession of the reference).

DeFatta teaches a DNA sequence comprising a constitutive promoter operably linked to a transcription sequence, when transcribed produces a mRNA sequence that comprises a translatable sequence encoding herpes Thymidine Kinase (HTK) (a conditional toxin) and an untranslated sequence comprising an untranslatable sequence with a stability of $\Delta G \geq 50$ Kcal/Mol (see p.95, second paragraph), such as the 5'untranslated sequence of FGF-2 (see p. 47, second paragraph); wherein the untranslated sequence inhibits translation of the toxin in the absence of eIF4E and wherein the untranslated sequence allows translation of HTK the presence of eIF4E (see p. 92-95 and Fig. 2); and wherein the DNA sequence (a BK vector which produces the indicated mRNA sequence, BK-UTK) is administered to a immunocompromised mouse such that the administration treats a breast cancer (MM2T cells).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on 9:00 a.m.- 6:00 p.m., Mon-Thurs.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER